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## Citation

Kociol, R. D., S. E. McNulty, A. F. Hernandez, K. L. Lee, M. M. Redfield, R. P. Tracy, E. Braunwald, C. M. O'Connor, and G. M. Felker. 2012. "Markers of Decongestion, Dyspnea Relief, and Clinical Outcomes Among Patients Hospitalized With Acute Heart Failure." *Circulation: Heart Failure* 6 (2) [December 18]: 240–245. doi:10.1161/circheartfailure.112.969246.

## Published Version

10.1161/CIRCHEARTFAILURE.112.969246

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Published in final edited form as:

*Circ Heart Fail.* 2013 March ; 6(2): . doi:10.1161/CIRCHEARTFAILURE.112.969246.

## Markers of Decongestion, Dyspnea Relief and Clinical Outcomes Among Patients Hospitalized with Acute Heart Failure

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### Abstract

**Background**—Congestion is a primary driver of symptoms in patients with acute heart failure (AHF), and relief of congestion is a critical goal of therapy. Monitoring of response to therapy through the assessment of daily weights and net fluid loss is the current standard of care, yet the relationship between commonly used markers of decongestion and both patient reported symptom relief and clinical outcomes are unknown.

**Methods and Results**—We performed a retrospective analysis of the randomized clinical trial -Diuretic Optimization Strategy Evaluation in Acute Heart Failure (DOSE-AHF), enrolling patients hospitalized with a diagnosis of acute decompensated heart failure (ADHF). We assessed the relationship between 3 markers of decongestion at 72 hours—weight loss, net fluid loss and % reduction in serum NT-proBNP level—and relief of symptoms as defined by the dyspnea visual analog scale area under the curve (VAS AUC). We also determined the relationship between each marker of decongestion and 60-day clinical outcomes defined as time to death, first re-hospitalization or ER visit. Mean age was 66 years, mean EF was 35% and 27% had EF  $\leq$  50%. Of the 3 measures of decongestion assessed, only % reduction in NT-proBNP was significantly associated with symptom relief ( $r=0.13$ ,  $P=0.04$ ). There was no correlation between either weight loss or net fluid loss and symptom relief, ( $r=0.04$ ,  $P=0.54$  and  $r=0.07$ ,  $P=0.27$ , respectively). Favorable changes in each of the 3 markers of decongestion were associated with improvement in time to death, re-hospitalization or ED visit at 60 days [weight: HR 0.91 (95% confidence interval 0.85, 0.97) per 4 lbs. weight lost; fluid HR 0.94 (0.90, 0.99) per 1000mL fluid loss; NT-proBNP HR 0.95 (0.91, 0.99) per 10% reduction]. These associations were unchanged after multivariable adjustment with the exception that % reduction in NT-proBNP was no longer a significant predictor (HR 0.97; 0.93, 1.02). Patients with 2 or 3 markers of decongestion (above the median value for each marker) had improved clinical outcomes versus those with 0 or 1 marker above the median value (39.0% versus 53.8%;  $P=0.03$ ).

**Conclusions**—Weight loss, fluid loss and NT-proBNP reduction at 72 hours are poorly correlated with dyspnea relief. However, favorable improvements in each of the 3 markers were

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### Disclosures

Dr. Hernandez reports research/grant support from Johnson & Johnson. No other relevant disclosures.

associated with improved clinical outcomes at 60 days. These data suggest the need for ongoing research to understand the relationships between symptom relief, congestion, and outcomes in patients with ADHF.

**Clinical Trial Registration**—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00577135.

## Keywords

heart failure; dyspnea; diuretics

Dyspnea is the most common chief complaint among patients hospitalized with acute decompensated heart failure (ADHF) and its relief is a primary goal of acute therapy<sup>1, 2</sup>. Moreover, relief of dyspnea is a key endpoint in clinical trials of therapies in ADHF<sup>3, 4</sup>. Presumably, dyspnea resolution is related to decreased pulmonary congestion<sup>5</sup> and guidelines recommend serial monitoring of markers of decongestion such as urine output and changes in body weight<sup>2, 6</sup>. Reductions in body weight and fluid loss may be related to decreased intravascular volume and should reflect decreased congestion. Elevations of natriuretic peptides released by myocardium in response to increased wall stress, represents a biochemical marker of increasing congestion<sup>7</sup>. Despite the intuitive concept that decreasing congestion should result in improvement in symptoms, information regarding the correlation between changes in markers of decongestion and symptom relief in patients with ADHF is sparse and the results have been inconsistent<sup>8, 9</sup>. Likewise, there are few data evaluating the relationship between markers of decongestion and short-term clinical outcomes<sup>10</sup>.

Understanding the relationship between markers of decongestion and dyspnea relief has implications at multiple levels including patient care, the mechanistic understanding of pulmonary congestion, the pathophysiology of dyspnea in heart failure, and the selection of clinical trial endpoints. To address these issues the present analysis used data from the DOSE trial to evaluate the relationships between markers of decongestion (weight loss, net fluid loss, reduction in BNP levels) symptom relief and 60-day clinical outcomes.

## Methods

### Data Source

The analysis used data from the NHLBI Heart Failure Network's sponsored DOSE trial (ClinicalTrials.gov number, NCT00577135), the study design and primary results of which have been published previously<sup>11, 12</sup>. Briefly, DOSE was a prospective, randomized, double blind, controlled trial, enrolling patients admitted to hospitals in 9 regional coordinating centers and their respective satellite sites with acute decompensated heart failure (ADHF). The study used a 2X2 factorial design randomizing patients to a strategy of high versus low dose furosemide treatment and continuous versus intermittent bolus furosemide administration.

### Study Population

A total of 308 patients at 26 sites were enrolled between March 2008 and November 2009. Patients admitted with a primary diagnosis of ADHF manifest by at least one sign and one symptom of ADHF were eligible for enrollment. They were required to have a history of chronic HF requiring outpatient oral loop diuretics. Patients with either reduced or preserved left ventricular ejection fraction (LVEF) were included. Patients with low BNP (<250 pg/mL) or NT-proBNP (<1000 pg/mL) were excluded, as were those with systolic blood pressures < 90 mmHg, serum creatinine > 3 mg/dL, or requiring vasoactive medications.

## Exposure variables

Three exposure variables representing potential markers of decongestion were analyzed. Weight loss was analyzed as the difference in weight from baseline to 72 hours in kilograms (kg). Net fluid loss was calculated as the difference between the sum of total fluid intake and total urine output over 72 hours in mL. Change in NT-proBNP was calculated as the % reduction from baseline to 72 hours.

## Outcomes

Symptom relief was determined by serial measurements of dyspnea at 6, 12, 24, 48, 72 and 96 hours post-randomization based on a dyspnea visual analog scale (VAS). The VAS scale asked patients to rate their level of dyspnea from 0–100, with the higher number indicating fewer symptoms. Change from baseline to 72 hours in dyspnea was calculated as the area under the curve (AUC) during that time interval. A higher dyspnea VAS AUC indicated a lower total burden of dyspnea over 72 hours.

The clinical outcome we analyzed was time to the composite of death, re-hospitalization or emergency department (ED) visit by 60 days.

## Statistical Analysis

Baseline characteristics were reported as frequency (%) for categorical variables and median (IQR) for continuous variables. Categorical variables were compared using likelihood ratio chi-squared tests, and continuous variables were compared using Wilcoxon signed rank tests. The relationships among markers of decongestion and between markers of decongestion and dyspnea were analyzed using general linear models. Pearson correlation coefficients were calculated.

Multivariable linear regression models were used to identify potential predictors of dyspnea relief at 72 hours among baseline variables. Candidate variables were selected based upon clinical relevance and published literature including age, gender, race, qualifying furosemide dose, ejection fraction, HF etiology, history of atrial fibrillation/flutter, diabetes, as well as baseline weight, systolic blood pressure, heart rate, oxygen saturation, jugular venous pressure, orthopnea, serum creatinine, and NT-proBNP.

Analyses comparing the number of markers of decongestion above the median value (0,1,2, or 3) versus time to the 60-day composite event of death, rehospitalization, or ER visit were performed using the Chi-square test.

Cox proportional hazards models were used to analyze the association between markers of decongestion and dyspnea relief at 72 hours and the 60-day composite clinical outcome of death, re-hospitalization or ED visit. The multivariable Cox model included the following covariates: age, gender, baseline creatinine, HF etiology, diabetes, ejection fraction, baseline sodium, baseline systolic blood pressure, baseline heart rate, qualifying furosemide dose, route of administration (bolus versus continuous) and intensification strategy (high versus low dose). A P-value of 0.05 was considered statistically significant. SAS version 9.2 (Cary, NC) was used for all analyses.

The DOSE study was approved by the Heart Failure Network Steering, Protocol Review and Data Safety Monitoring Committees and was approved by each participating site's institutional review board. All patients provided written informed consent.

## Results

Among 308 patients enrolled, net fluid loss at 72 hours, net weight loss at 72 hours, and NT-proBNP change at 72 hours were available for 242, 294, and 247 patients, respectively. Characteristics of patients are displayed in Table 1. The median age of the study population was 68 years. Approximately three-quarters of the population were white and three-quarters were male. The median left ventricular ejection fraction was 30% and 27% of patients had an ejection fraction  $\geq 50\%$ . Approximately half of the population had an ischemic etiology for their heart failure, a history of atrial fibrillation or flutter, and a history of diabetes. Most patients had orthopnea and elevated jugular venous pressure at baseline. The median net fluid loss, net weight loss, and percent reduction in NT-proBNP at 72 hours were 3.8 L (IQR 1.9 - 6.0; min, max -2.8, 15.6), 6.5 lbs. (2.6 - 11.7; -42.3, 56.4), and 24.3% (-0.9 - 48.4; -199.5, 88.7), respectively.

### Relationship between markers of decongestion and dyspnea

Net fluid loss at 72 hours and net weight loss at 72 hours were modestly correlated ( $r=0.46$ ,  $P<.0001$ ). The percent reduction in NT-proBNP at 72 hours did not significantly correlate with either net fluid loss ( $r=0.11$ ,  $P=0.11$ ) or net weight loss ( $r=0.11$ ,  $P=0.08$ ). Table 2 shows the correlation between markers of decongestion and 72 hour dyspnea VAS AUC. No statistically significant correlation existed between net fluid loss or net weight loss and dyspnea VAS AUC at 72 hours. The percent change in NT-proBNP at 72 hours was modestly correlated with dyspnea VAS AUC ( $r=0.13$ ,  $P=0.04$ ).

When dichotomizing each marker of decongestion as above or below the median for the group, there was no relationship between the number of markers above the median (0, 1, 2 or 3) and dyspnea VAS AUC at 72 hours ( $P=0.47$ ).

### Baseline characteristics predicting improved dyspnea at 72-hours

Among baseline characteristics considered in a multivariable linear regression model to identify predictors of improvement in dyspnea at 72 hours, only the presence of orthopnea at baseline was associated with lower dyspnea VAS AUC (worse dyspnea) at 72 hours ( $P=0.03$ ).

### Relationship between 72-hour dyspnea VAS AUC and clinical outcome

The dyspnea VAS AUC (for every 100 point increase) at 72-hours was associated with a small improvement in the 60-day clinical outcome of time to first ED visit, rehospitalization or death in a univariate Cox model (HR 0.99;  $P=0.01$ ). However, after adjustment for baseline characteristics, the association was no longer significant (HR 0.99;  $P=0.08$ ).

### Relationship between markers of decongestion and clinical outcome

Changes in each of the 3 markers of decongestion were significantly associated with time to first emergency department visit, re-hospitalization or death by 60 days (Table 3). Each 1000mL increment in net fluid output was associated with a 6% reduction in risk of the 60-day combined clinical endpoint. Each 4 lb. loss of weight at 72 hours was associated with a 9% reduction in the risk and each 10% reduction in NT-proBNP from baseline was associated with a 5% reduction in risk. After multivariable adjustment, there was a statistically significant association between both the net fluid loss and weight loss markers and reduction in the risk of time to the composite clinical endpoint. After adjustment for covariates, percent change in NT-proBNP at 72 hours was no longer significantly associated with the composite clinical endpoint.

Dichotomizing each marker of decongestion as above or below the median value, we classified patients (among those with complete data) as being above the median for 0, 1, 2 or all 3 markers of decongestion. 211 patients were available for this analysis. In a stepwise fashion, those with increasing numbers of markers of successful decongestion (above the median value) had decreased rates of reaching the clinical endpoint of ED visit, rehospitalization or death within 60 days (Figure). Probability of survival free of death, HF hospitalization or ED visit for those with 0, 1, 2 and 3 markers of decongestion were 67%, 64%, 46%, and 38%, respectively, (Log rank P-value 0.05).

## Discussion

Understanding both the relationship between measures of decongestion and symptom relief among patients with ADHF is relevant for both patient care and investigation of new therapies<sup>3, 4</sup>. In the present study, neither weight loss, fluid loss, nor change in natriuretic peptide levels were closely correlated with improvement in dyspnea as measured in a multicenter randomized clinical trial. Among baseline admission variables only orthopnea on admission was associated with 72-hour dyspnea. However, these decongestion markers do correlate with short-term clinical outcomes and those with multiple markers of decongestion have better outcomes. Potential explanations for these findings include a true lack of correlation between changes in decongestion measures and dyspnea relief, poor sensitivity of the VAS measure of dyspnea or, likely, some combination of these factors.

### Clinical Utility of Markers of Decongestion

Net fluid loss and weight loss are both measures of changes in total body fluid<sup>8</sup>. The correlation between these two markers was only moderate in our study, despite the fact that they ostensibly measure the same process. However, measurement of net fluid loss in hospitalized patients is often inaccurate because of inadvertently discarded urine, assumptions regarding fluid volume in food products, and insensible losses. Error may be introduced into the measure of body weight due primarily to imprecision of the scale or using different scales at different time points. Given these considerations, it is not unexpected that weight loss and net fluid loss would not be perfectly correlated, but they should be reasonable approximations of total body fluid loss if done carefully. Nevertheless, we failed to find a correlation between each of these measures and dyspnea relief at 72 hours. One potential explanation is that dyspnea relief requires more than just volume removal, but rather reduced pulmonary artery wedge pressure. The latter is not only a function of left ventricular end-diastolic volume (preload) but also of afterload and ventricular compliance<sup>13</sup>. For example, a patient with pulmonary congestion in the setting of marked hypertension may achieve substantial symptom resolution with nitrate therapy resulting in venodilation (preload reduction) and arterial vasodilation (afterload reduction), even in the absence of changes status<sup>5</sup>.

### Correlation Between Markers of Decongestion and Dyspnea

Another potential explanation for the lack of correlation between weight loss, net fluid loss and dyspnea relief may be related to the poor ability of currently used dyspnea instruments to accurately capture symptom relief<sup>14</sup>. This has been an active topic in the heart failure literature as acute symptom relief is an important endpoint in trials of new therapies for ADHF<sup>3, 4, 14</sup>. A variety of potential tools to assess dyspnea relief have been used in prior studies, including visual analog scales, Likert scales, and numerical rating scales. Indeed, nesiritide was approved by the Food and Drug Administration in 2001 for the treatment of ADHF, based in part on a small improvement in dyspnea score over placebo based on a Likert scale<sup>15</sup>. Investigators have argued that instruments to measure dyspnea presently used in clinical trials lack sensitivity and are poorly validated<sup>14</sup>. In the present analysis, we



measured dyspnea as area under the curve (over time) of individual measurements based on a visual analog scale<sup>11</sup>. Recently investigators have begun to study the concept of provoked dyspnea – that is, using postural and exercise maneuvers to discern a patient's underlying level of dyspnea<sup>16</sup>. Hypothetically, this measurement of dyspnea at rest and with provocation should be more sensitive to treatment effects on dyspnea than a simple, scaled, measurement of dyspnea at a given time point which is not controlled for posture and most commonly - but not always - performed at rest in a hospital bed<sup>14</sup>. An ongoing study sponsored the National Heart Lung and Blood Institute's Heart Failure Network is exploring the sensitivity of a provoked dyspnea scale to assess changes in dyspnea over time with treatment among patients hospitalized with ADHF (Renal Optimization Strategies Evaluation in Acute Heart Failure - ROSE-AHF. ClinicalTrials.gov NCT01132846).

### Comparison with Prior Studies

Previous studies addressing these questions have had variable results. The Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) trial comparing ultrafiltration and intravenous diuretic therapy reported significantly greater reduction in body weight and increased fluid loss in the ultrafiltration arm; however there was no difference in the dyspnea score between the two therapies<sup>8</sup>. In contrast, a post-hoc analysis of the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial did demonstrate a statistically significant, albeit weak, correlation between weight loss and dyspnea ( $r=0.20$ ). However, there was no correlation between weight loss and subsequent clinical outcomes<sup>9</sup>. Similarly, in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) ESCAPE trial there was no association between weight loss and inpatient or outpatient clinical events. However, those in the highest tertile of weight loss had a significantly decreased orthopnea score.<sup>10</sup>

This study found an association between improvement in dyspnea at 72 hours and clinical outcomes at 60 days. These data are similar to prior work by Metra and colleagues demonstrating a relationship between dyspnea improvement and post-discharge clinical outcomes<sup>17, 18</sup>. However, in the current study, this association was no longer statistically significant after adjusting for baseline characteristics.

### Markers of Decongestion and Short Term Clinical Outcomes

The finding of a moderate correlation between both weight loss and net fluid loss and 60-day death, re-hospitalization or emergency department visit differs from findings in the ESCAPE trial in which there was no correlation between weight loss and clinical outcomes. One potential reason for the difference is that the ESCAPE cohort was sicker and, hence, their degree of illness may have mitigated the effects of volume removal as an independent predictor of clinical outcomes<sup>10</sup>. In comparison, patients undergoing ultrafiltration in the UNLOAD trial, had decreased risk of 90-day clinical events (re-hospitalization, unscheduled physician visits) in conjunction with greater average volume removal<sup>8</sup>.

The absence of a significant relationship (adjusted for baseline variables) between percent change in NT-proBNP at 72 hours and 60-day clinical outcomes was unexpected as several small studies have previously documented such a relationship<sup>19–22</sup>. Given that there still appeared to be a trend towards improved outcomes among those with greater reductions, this finding may represent a limitation of our sample size.

Finally, the study found that for each additional marker of decongestion greater than the median value, event rates improve noticeably. This suggests that a strategy of evaluating all

available data concerning a given patient's volume status is preferable than focusing on only one such as the change in weight.

## Clinical Implications

Our study has several important clinical implications. Individual markers of decongestion as currently measured them do not correlate well with symptom relief. This finding may reflect the heterogeneity of acute heart failure syndromes and/or the lack of sensitivity of current dyspnea instruments. However, multiple markers of decongestion in the same patient are associated with improved clinical outcomes such as fewer ED visits, readmissions or death compared to fewer or no markers of decongestion. These results suggest that measuring markers of decongestion continue to have clinical utility in the care of hospitalized patients, but should be interpreted in the context of patient reported symptoms and physical examination findings.

## Limitations

This was a post-hoc retrospective observational study of a clinical trial. There may be residual or unmeasured confounding even after multivariable adjusting. Additionally, the sample size was relatively small which decreased our ability to detect a difference when performing the analysis. Measurement errors may have been introduced in determining net fluid balance based on human error. For example, urine output may not fully represent all fluid loss given other insensible losses. Likewise, utilization of different weight scales or non-standardization of time-of-day for weight measurement may have introduced error into the weight loss variable.

However, our results are meant to inform real-world practice where such measurement is likely to occur. Since this was a clinical trial, exclusion criteria were implemented in part related to stability (systolic blood pressure > 90 mmHg, lack of vasoactive medications) and renal function (Serum Creatinine < 3 mg/dL). These exclusions could limit the generalizability of these results to less stable patients or those with marginal renal function.

## Conclusion

Among three markers of decongestion, net fluid loss at 72 hours, weight loss at 72 hours and % reduction in NT-proBNP at 72 hours, only % reduction in NT-proBNP was correlated, albeit modestly, with symptom relief. Among several baseline characteristics considered, only orthopnea at admission was associated with change in dyspnea at 72 hours. Finally, after adjustment for potential confounders, only net fluid loss and weight loss at 72 hours were modestly associated with time to death, re-hospitalization or ED visit at 60 days. These data underscore the current knowledge gaps regarding the relationship between dyspnea, congestion, and outcomes in patients with ADHF. Greater understanding of the biology of dyspnea and decongestion in ADHF will be critical if these concepts are to continue to be targets for drug development.

## Acknowledgments

### Sources of Funding

National Institutes of Health, National Heart, Lung, and Blood Institute. ClinicalTrials.gov number, NCT00577135.

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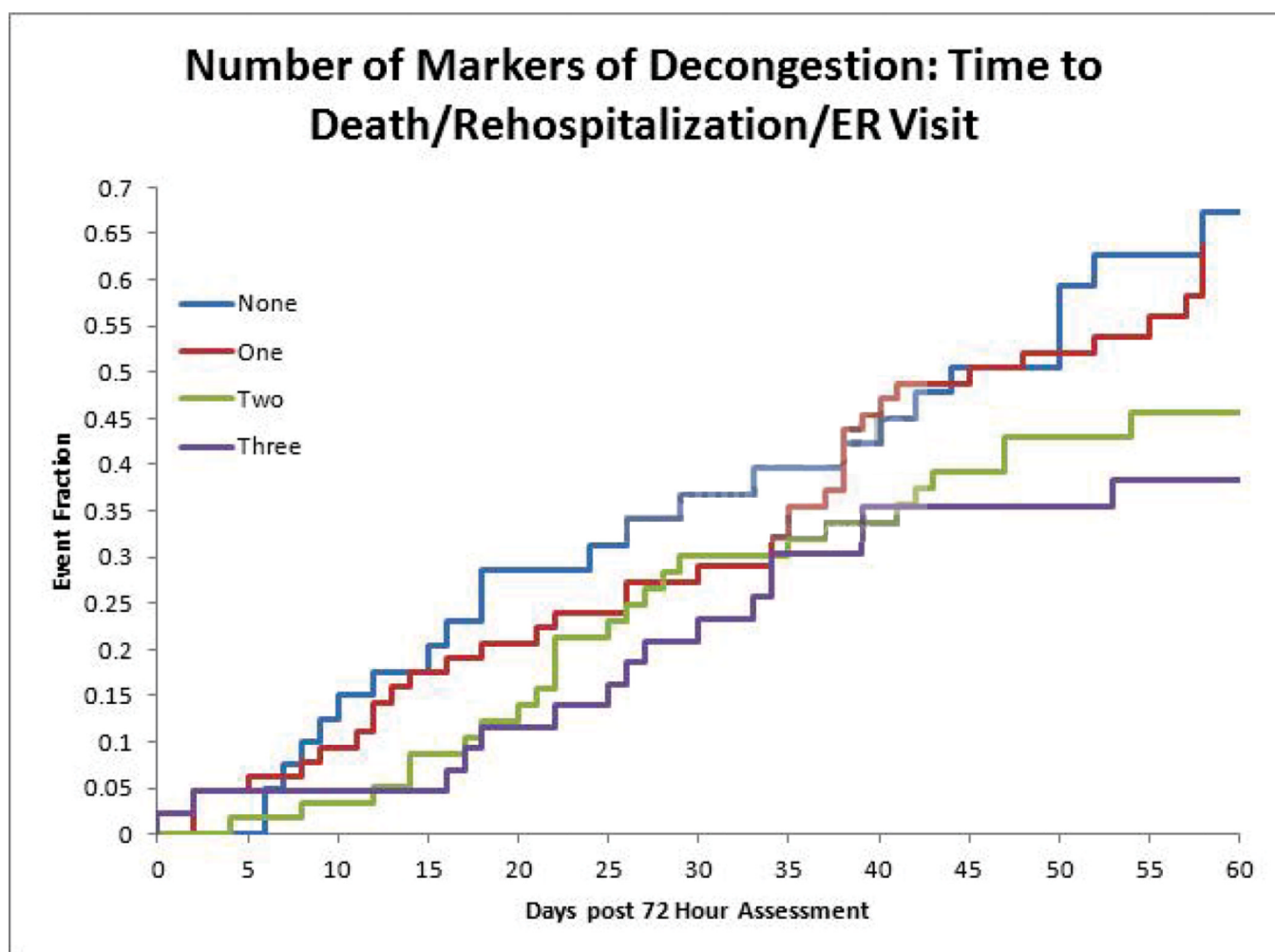
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**Figure.**

Relationship Between Number of Markers of Decongestion Above Median \* and time to 60-day Risk of ED Visit, Rehospitalization or Death. (ED: emergency department).

\* Median net fluid loss 3.8 L, median net weight loss 6.5 lbs, median % reduction in NT-proBNP 24.3%.

**Table 1**

## Baseline characteristics

Variable <sup>1</sup>	All Patients N=308
Age, years	68 (56, 77)
Male	226 (73.4)
White race	222 (72.1)
Weight, lbs.	206 (176, 242)
Baseline furosemide dose, mg	120 (80, 160)
Left ventricular ejection fraction, %	30 (20, 50)
Ischemic etiology	176 (57.1)
Atrial fibrillation/ flutter	162 (52.6)
Baseline systolic blood pressure, mmHg	115 (104, 132)
Baseline heart rate, bpm	76 (69, 85)
Baseline oxygen saturation, %	96 (94, 98)
JVP 8 cm	267 (91.4)
Orthopnea 2 pillows	229 (77.9)
Sodium, mEq	139 (136, 141)
BUN, mg/dL	31 (20, 50)
Creatinine, mg/dL	1.43 (1.10, 1.83)

<sup>1</sup> Categorical variables reported as frequency (percent) and continuous variables reported as median (interquartile ratio).

**Table 2**

Correlation between markers of decongestion and change in dyspnea VAS AUC at 72 hours

Marker of Decongestion	N	r	P-value
Net fluid loss at 72 hours	239	0.07	0.27
Weight loss at 72 hours	291	0.04	0.54
% reduction in NT-proBNP at 72 hours	246	0.13	0.04

**Table 3**

Unadjusted and adjusted relationship between change in markers of decongestion at 72 hours and 60-day risk of emergency department visit, re-hospitalization, or death.

Marker of Decongestion	Unadjusted HR <sup>1</sup> (95% CI)	Adjusted HR <sup>2</sup> (95% CI)
Net fluid loss at 72 hours (per 1000 ml)	0.94 (0.88, 0.99)	0.93 (0.88, 1.00)
Weight loss at 72 hours (per 4 lbs)	0.91 (0.85, 0.97)	0.92 (0.85, 0.98)
% reduction in NT-proBNP at 72 hours (per 10%)	0.95 (0.91, 0.99)	0.97 (0.93, 1.02)

<sup>1</sup> Hazard ratio from the unadjusted cox regression model

<sup>2</sup> Hazard ratio from the adjusted cox regression mode